

The Angiographic and Clinical Benefits of Mibefradil in the Coronary Slow Flow Phenomenon

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OBJECTIVES	The aim of the study was to assess the angiographic and clinical benefits of the calcium T-channel blocker, mibefradil, in the coronary slow flow phenomenon (CSFP).
BACKGROUND	The CSFP is characterized by delayed vessel opacification on angiography (Thrombolysis In Myocardial Infarction [TIMI]-2 flow) in the absence of obstructive epicardial coronary disease and is often associated with recurrent chest pain.
METHODS	A total of 10 CSFP patients (46 ± 9 years) underwent angiography before and 30 min after 50 mg mibefradil; off-line blinded analysis of angiographic data included comparisons of epicardial vessel diameter, TIMI flow grade and TIMI frame count. We also performed a randomized, double-blind, placebo-controlled, cross-over study to examine the long-term efficacy of mibefradil 100 mg/day on the frequency of total angina, prolonged angina (i.e., persisting >20 min) episodes, and sublingual nitrate consumption, during consecutive one-month treatment periods in 20 patients (age 51 ± 12 years) with the CSFP.
RESULTS	Without changing epicardial vessel diameter or rate-pressure product, mibefradil reduced the number of vessels exhibiting TIMI-2 flow from 18 to 5; furthermore, mibefradil significantly improved the TIMI frame count only in those vessels exhibiting TIMI-2 flow ($28 \pm 18\%$, $p < 0.005$). Compared with placebo, mibefradil significantly reduced total angina frequency by 56% ($p < 0.001$), prolonged episodes of angina by 74% ($p < 0.001$), and sublingual nitrate consumption by 59% ($p < 0.01$); furthermore, mibefradil improved physical quality of life as assessed by the Health Outcome Study Short Form-36.
CONCLUSIONS	These angiographic and clinical improvements produced by mibefradil support a microspastic pathogenesis of the CSFP. (J Am Coll Cardiol 2004;44:57–62) © 2004 by the American College of Cardiology Foundation

The coronary slow flow phenomenon (CSFP) is a coronary microvascular disorder characterized by the delayed passage of contrast in the absence of obstructive epicardial coronary disease. It is well recognized by coronary angiographers but has largely been considered an angiographic curiosity and received little attention despite previous studies demonstrating coronary microvascular dysfunction (1–3).

The presentation of the CSFP differs from other coronary microvascular disorders, with most patients undergoing angiography after admission with an acute coronary syndrome (4), accounting for 4% of unstable angina admissions (5). The clinical course is quite debilitating, with over 80% of patients experiencing recurrent chest pain, necessitating readmission to the coronary care unit in almost 20% (4).

From clinical experience, conventional antianginal therapy is of limited benefit in the chronic management of these patients, with the exception of the unique calcium T-channel blocker, mibefradil. The aim of this study was to evaluate the efficacy of mibefradil in the management of the

CSFP by examining the acute angiographic effects of mibefradil on delayed vessel opacification and its chronic antianginal effects in affected patients.

METHODS

Two separate studies were conducted to examine the effects of mibefradil in the CSFP: 1) an acute angiographic study; and 2) a chronic antianginal efficacy study. In both studies, CSFP was defined by the consensus of at least two independent observers on the basis of: 1) angiographically normal or near-normal (<40% stenosis) epicardial coronary arteries; and 2) Thrombolysis In Myocardial Infarction (TIMI)-2 flow (i.e., requiring ≥ 3 beats to opacify the distal vasculature) (6) in at least one major vessel. The study exclusion criteria were: 1) coronary slow flow after a coronary intervention; 2) left ventricular systolic dysfunction (ejection fraction <50%); 3) sinus node disease; and 4) concurrent therapy with medications metabolized via cytochrome P450 3A4, which is inhibited by mibefradil (7). The study was approved by the institutional ethics committee, and informed consent was obtained from all patients.

Acute angiographic response to mibefradil. Ten patients with documented coronary slow flow underwent a prospectively designed investigation with blinded end point analysis to examine the hypothesis that mibefradil acutely accelerates distal vessel opacification in affected patients. All patients

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Abbreviations and Acronyms

CSFP = coronary slow flow phenomenon
CTFC = corrected TIMI frame count
ECG = electrocardiogram
LAD = left anterior descending artery
SF-36 = Health Outcome Study Short Form-36
TIMI = Thrombolysis In Myocardial Infarction

had been admitted with a clinical diagnosis of unstable angina and treated with verapamil, aspirin, intravenous nitrates, and heparin therapy. These medications were continued during the coronary angiographic procedure.

Coronary angiography was performed using 6-F Judkins catheters with images acquired at 12.5 frames/s on a Philips Integra angiographic system (Philips, the Netherlands). After baseline angiographic views, patients chewed then swallowed a 50-mg mibefradil tablet. After a 30-min observation period during which heart rate, blood pressure, and 2-lead electrocardiogram (ECG) were continuously monitored, angiographic views were repeated. The baseline and 30-min images were analyzed off-line by two independent observers blinded to the patient and image sequence.

Proximal and distal epicardial artery diameters were assessed for each of the three major coronary arteries using automated edge detection software with pincushion distortion correction and calibrated for the diagnostic catheter diameter. The TIMI flow grade and TIMI frame count were assessed for each vessel utilizing criteria defined by Chesebro *et al.* (6) and Gibson *et al.* (8), respectively.

Corrected TIMI frame counts (CTFC) were calculated to account for the greater length of the left anterior descending artery (LAD) utilizing previously established methodology (8). The correction factor was determined by analysis of 30 patients with satisfactory angiographic views, who had angiographically smooth epicardial coronary arteries with TIMI-3 flow and normal left ventricular systolic function (ejection fraction $\geq 50\%$). The mean (\pm SD) TIMI frame count for the circumflex and right coronary arteries were similar (11 ± 3 frames and 10 ± 3 frames, respectively) and significantly less than the LAD (19 ± 5 frames, $p < 0.001$). Dividing the mean TIMI frame count of the LAD by the combined value of the shorter vessels attained a correction factor of 1.7, consistent with values previously published (8). Hence, the CTFC for the LAD in this control group was 11 ± 3 frames.

Additionally, a limited time-control study was performed to determine if CTFC changed spontaneously during the 30-min observation period. Six further patients with the CSFP underwent baseline and 30-min angiographic views without the administration of mibefradil. Images were assessed in conjunction with the above pre-/post-mibefradil images so that the observer was blinded in relation to image sequence and whether mibefradil had been administered.

Chronic antianginal efficacy of mibefradil. Twenty-one patients with the CSFP who experienced angina at least 3

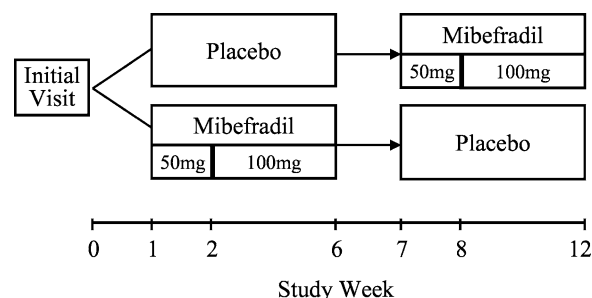


Figure 1. Study protocol. Summary of the 12-week study protocol including double-blind randomization to placebo/mibefradil 50 mg therapy for one week followed by four weeks of placebo/mibefradil 100 mg therapy with cross-over to the alternative therapy after a one-week washout period.

times a week were recruited into this investigation, including 3 of the 10 patients who participated in the acute angiographic response to mibefradil study. This randomized, double-blind, placebo-controlled, cross-over study assessed the hypothesis that mibefradil reduces total angina frequency in patients with the CSFP.

The study protocol for this investigation is summarized in Figure 1. After an initial visit when clinical history and informed consent were obtained, patients ceased their usual antianginal therapy (except sublingual nitrates). One week later, they were randomized to placebo/mibefradil therapy using a computer-generated algorithm. Treatment sequence was known only to the hospital investigational drugs pharmacist who had no contact with the patients.

After one week of mibefradil 50 mg/placebo therapy, patients were reviewed for tolerance of this dose, and dosage increased to the 100 mg/placebo dosage. Patients continued on this target dose for a four-week period after which they were clinically reassessed and commenced a one-week washout phase. Thereafter, patients crossed-over to the alternative mibefradil 50 mg/placebo treatment. If severe recurrent chest pain occurred on the randomized treatment, incremental open-labeled antianginals could be initiated in the following sequence: isosorbide mononitrate (slow release) 60 mg, 120 mg, and then nifedipine controlled-release 60 mg as once daily medications.

Throughout the study period, patients maintained an angina diary recording the frequency and duration of anginal episodes as well as sublingual nitrate consumption. At each clinic visit, the diary was reviewed, changes in non-study medication noted, adverse effects documented, and resting heart rate and blood pressure recorded. In the last week of each of the randomized treatment phases, the following parameters were assessed: 1) resting 12-lead ECG; 2) 12-channel, 24-h ambulatory ECG monitoring for ST-segment changes (utilizing Rozinn Holter for Windows Version 4.1 software); 3) C-reactive protein (nephelometric assay; Dade-Behring, New York) and troponin-I (immunoassay; Dade-Behring); 4) patient compliance by pill count; and 5) quality of life assessment utilizing the well-validated (9) Health Outcome Study Short Form 36 (SF-36).

Table 1. Hemodynamic Parameters and Coronary Diameters Pre- and Post-Mibefradil in 10 Patients With the CSFP

	Pre-Mibefradil	Post-Mibefradil	% Change	p Value
Hemodynamics				
Heart rate (beats/min)	71 ± 10	69 ± 11	−3 ± 7	0.3
Mean arterial pressure (mm Hg)	91 ± 6	94 ± 7	4 ± 7	0.2
Rate-pressure product (beats/min mm Hg × 10 ³)	9.2 ± 1.7	9.2 ± 2.0	−1 ± 14	0.7
Coronary artery diameters				
LAD				
Proximal (mm)	3.52 ± 0.72	3.68 ± 0.82	5 ± 8	0.2
Distal (mm)	1.32 ± 0.32	1.26 ± 0.36	−5 ± 10	0.3
Cx				
Proximal (mm)	3.93 ± 0.59	3.98 ± 0.61	1 ± 3	0.3
Distal (mm)	1.34 ± 0.23	1.34 ± 0.21	1 ± 4	0.8
RCA				
Proximal (mm)	4.40 ± 0.77	4.50 ± 0.75	2 ± 3	0.053
Distal (mm)	1.69 ± 0.29	1.76 ± 0.24	4 ± 5	0.056
Coronary flow indexes				
Vessels with the CSFP (n)	18	5	−72	0.0006
CTFC in vessels initially with TIMI-2 flow (frames)	36 ± 7	25 ± 6	−28 ± 18	0.0001
CTFC in vessels initially with TIMI-3 flow (frames)	20 ± 8	19 ± 8	−7 ± 35	0.3

*Mibefradil was administered as a single 50-mg oral dose.

CSFP = coronary slow flow phenomenon; CTFC = corrected TIMI frame count; Cx = circumflex artery; LAD = left anterior descending artery; RCA = right coronary artery; TIMI = Thrombolysis In Myocardial Infarction.

The primary end point of this investigation was the frequency of angina episodes recorded in the patient's angina diary. Secondary end points were frequency of prolonged anginal episodes (>20 min), sublingual nitrate consumption, ST-segment changes on ambulatory ECG, changes in cardiac markers, and SF-36 scores. The sample size was calculated on the basis of a survey of eight slow flow patients in whom mibefradil therapy reduced angina frequency by $90 \pm 14\%$ over a six-month period. Based on this observation, 17 coronary slow flow patients would need to be recruited to detect a 15% reduction in chest pain frequency with a 90% power where $p < 0.01$ (two-tailed). **Data analysis.** Continuous variables were expressed as mean ± SD, unless otherwise indicated. Statistical significance was considered at the $p < 0.05$ level. Comparisons of the baseline and 30-min angiographic data were made with chi-square test and paired Student *t* test for categorical and continuous data, respectively.

The clinical investigation of mibefradil's chronic antianginal efficacy was made using appropriate cross-over trial methodology (10). Thus, blinded analysis of the angina diary end points were performed by comparison between patients with respect to treatment order utilizing Mann-Whitney *U* tests. Similarly, comparisons of secondary end point parametric data were performed with the two-sample *t* test for two independent samples applied appropriately to average differences and sums of the responses within and between patients. Comparisons of the SF-36 scores were made with analysis of variance for repeated samples.

RESULTS

Acute angiographic response to mibefradil. Among the 10 patients (mean age of 46 ± 9 years; 9 males) participating in the angiographic study, baseline angiography dem-

onstrated smooth epicardial coronary arteries in all except one patient who had a 40% stenosis in the LAD and an ectatic right coronary artery. Of the 30 major epicardial coronary vessels systematically assessed, 18 exhibited TIMI-2 flow at baseline with the most commonly affected being the LAD (50%), followed by the right coronary (28%) and circumflex (22%) arteries.

Oral administration of 50 mg mibefradil was well-tolerated and was not associated with a significant change in heart rate, mean arterial pressure, rate-pressure product, or epicardial coronary artery diameter during the 30-min observation period (Table 1). However, the coronary flow indexes improved after mibefradil (Fig. 2), with abolition of the CSFP in 13 of the 18 vessels initially exhibiting the phenomenon. Furthermore, analysis of the CTFC (Table 1) demonstrates that the effects of mibefradil in accelerating flow were significantly greater ($p < 0.05$) in vessels initially exhibiting the CSFP ($28 \pm 18\%$ improvement in CTFC) than in those vessels exhibiting TIMI-3 flow ($7 \pm 35\%$ improvement in CTFC) (Fig 3).

In contrast, among the six time-control patients, there was no significant change in CTFC over the 30-min period both in the vessels that initially exhibited the CSFP ($1 \pm 21\%$, $p = 0.98$) and those initially with TIMI-3 flow ($8 \pm 18\%$, $p = 0.19$).

Chronic antianginal efficacy of mibefradil. Over a 12-month period, 21 patients were recruited, with 1 patient withdrawn from the study due to visit noncompliance two weeks after recruitment. The coronary risk factor profile of the remaining 20 patients (mean age = 51 ± 12 years; 13 males) included cigarette smoking in 4 (20%), hypertension in 5 (25%), diabetes in 3 (15%), and hypercholesterolemia (total cholesterol >212 mg/dl) in 11 (55%), although only 2 patients received lipid-lowering therapy. Index angiography

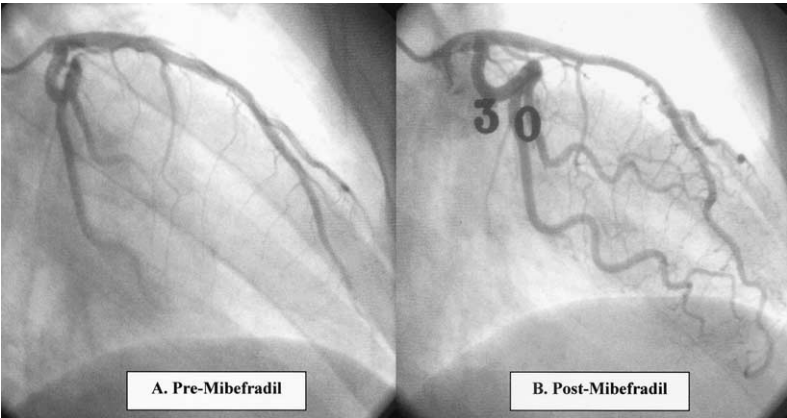


Figure 2. Acute angiographic response to mibefradil. An example of the angiographic response to a single oral dose of 50 mg mibefradil in a patient with the coronary slow flow phenomenon (CSFP). The angiographic snapshots presented were taken exactly three heart beats after contrast filled the width of the left main coronary artery. **(A)** Recorded before mibefradil administration and demonstrates incomplete opacification of the left anterior descending and circumflex arteries at three beats, thereby confirming the diagnosis of the CSFP. **(B)** Demonstrates improved vessel opacification 30 min after mibefradil administration.

demonstrating the CSFP was undertaken after an acute coronary syndrome presentation in 15 patients (75%). Angiography demonstrated smooth epicardial vessels in 16 patients (80%), minor ectasia in 2, (10%) and a minor nonobstructive (<40%) lesion in the remainder. Of the 60 major epicardial vessels, 33 exhibited the CSFP, with the LAD involved in all patients. Left ventricular systolic function on echocardiography was normal in all patients, and four (25%) had borderline criteria for left ventricular hypertrophy. Eighteen patients underwent standard exercise stress testing, but only five (28%) showed ST-segment changes consistent with ischemia. None of 10 patients who underwent stress myocardial scintigraphy showed evidence of inducible ischemia.

All of the 20 patients achieved and tolerated the target

dose of 100 mg mibefradil. Patient compliance was over 90% on pill count in all patients except for one with 86% during active treatment. There were no significant differences in prospectively examined potential adverse effects between mibefradil and placebo therapy.

Compared with placebo, mibefradil 100 mg produced a significant fall in systolic blood pressure, diastolic blood pressure, and rate-pressure product (Table 2). There was a trend towards heart rate reduction although this did not achieve statistical significance (Table 2). Mibefradil did not alter the corrected QT interval compared with placebo treatment ($QT_c = 410 \pm 30$ ms vs. 407 ± 36 ms, respectively; $p = 0.6$).

The major end point findings from the angina diary are summarized in Table 3. Mibefradil 100 mg significantly

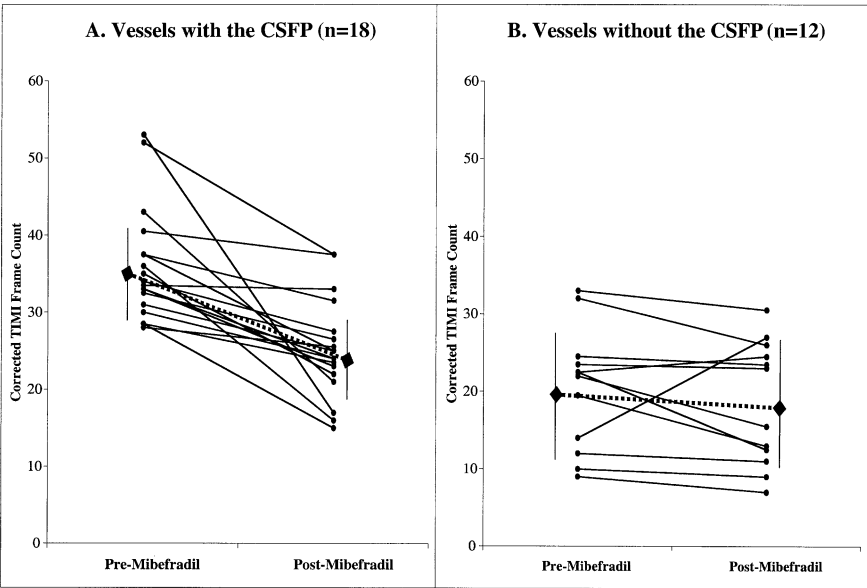


Figure 3. Profile plot of angiographic response to mibefradil. The Thrombolysis In Myocardial Infarction (TIMI) frame counts were assessed by two blinded independent observers immediately before and 30 min after a single oral 50 mg mibefradil dose in 10 patients with the coronary slow flow phenomenon (CSFP). Mibefradil selectively improved the angiographic response in the 18 vessels initially exhibiting the CSFP **(A)** ($p < 0.005$) and had little effect in the 12 vessels with TIMI-3 flow **(B)**.

Table 2. Changes in Hemodynamic Parameters During Four Weeks of Placebo and Mibefradil 100 mg Therapy in 20 Patients With the CSFP

Parameters	Placebo	Mibefradil	p Value
ΔPulse Rate (beats/min)	0 ± 15	−6 ± 10	0.131
ΔSystolic BP (mm Hg)	3 ± 10	−9 ± 11	<0.001
ΔDiastolic BP (mm Hg)	3 ± 10	−5 ± 9	0.020
ΔRate-pressure product (beats/min · mm Hg × 10 ³)	0.2 ± 2.2	−1.6 ± 2.0	0.005

BP = blood pressure; CSFP = coronary slow flow phenomenon.

reduced total angina frequency by 56%, prolonged episodes of angina by 74%, and sublingual nitrate consumption by 59%. During the study period, there were six hospital readmissions (among five patients) for uncontrolled angina requiring intravenous nitrates. Only one of these occurred with the patient on maximal mibefradil therapy. Three patients required incremental open-label antianginals because of severe recurrent chest pain on the randomized treatment. Two patients required combined isosorbide mononitrate and nifedipine in both cross-over phases. A third patient required isosorbide mononitrate while on placebo therapy alone.

Twenty-four hour ambulatory ECG Holter monitoring was undertaken in all patients in the last week of each randomized treatment although the data were incomplete in one patient during the placebo phase. Consistent with the aforementioned findings, more patients experienced chest pain when ambulatory ECG monitoring was undertaken on placebo as compared with mibefradil therapy (53% vs. 20% of CSFP patients, respectively; $p < 0.05$). Despite this, no patient demonstrated significant ST-segment changes (i.e., >1 mm ST-segment change for >1 min) during either treatment phase. Furthermore, there was no significant change between placebo and mibefradil therapy in other cardiac markers including C-reactive protein (3 ± 3 mg/l vs. 3 ± 4 mg/l, respectively; $p > 0.05$) and troponin-I (0.0 ± 0.1 μg/l vs. 0.0 ± 0.1 μg/l, respectively; $p > 0.05$) despite episodes of prolonged angina.

Table 4 summarizes the findings from the eight health concepts of the SF-36 survey during placebo and active treatment. Mibefradil significantly improved all elements of physical function, resulting in a significant increase in overall physical health summary score compared with placebo (Table 4). Although vitality scores increased significantly after mibefradil, there was no significant change in overall mental health scores (Table 4).

DISCUSSION

This angiographic and therapeutic investigation has demonstrated that the calcium T-channel blocker mibefradil

markedly improves angiographic coronary flow rates in patients with the CSFP, and has a major effect in ameliorating anginal symptoms resulting in improved physical well being. As the CSFP is frequently associated with rest angina (4), the findings are consistent with the hypothesis that the CSFP represents a distinct microspastic form of angina pectoris.

While previous investigators (1,2) have implicated coronary microspasm in the pathogenesis of the CSFP, this is the first controlled trial of pharmacotherapy in such patients. Mibefradil was chosen for this investigation on the basis of encouraging initial open-label experience. This decision was vindicated by the findings of this study, which showed a marked reduction in total and prolonged spontaneous anginal episodes resulting in an improved quality of life and a trend towards fewer hospitalizations with unstable angina. Whether other antianginal agents are effective in this condition requires further studies. Our clinical experience in managing patients with the CSFP suggest that organic nitrates, beta-adrenoceptor antagonists, and conventional calcium L-channel blockers are of limited benefit in controlling symptoms. Dipyridamole has been reported to be effective in an open-label study (11).

The unique pharmacologic properties of mibefradil may account for its efficacy in the CSFP. Gustafsson *et al.* (12) recently demonstrated an absence of calcium L-channels and an abundance of T-channels in rat microvessels. This may account for the persistence of the CSFP on angiography despite background L-channel blockade with verapamil and its subsequent resolution with calcium T-channel blockade by mibefradil.

Mibefradil was withdrawn from general therapeutic availability by the manufacturing company primarily because of its inhibition of cytochrome P450 3A4, resulting in potential accumulation of coadministered drugs (particularly simvastatin) metabolized via this pathway. By avoiding potentially interacting drugs (e.g., utilizing pravastatin, which is predominantly metabolized via an alternative pathway [13]),

Table 3. Median Values (25%, 75% Interquartile Ranges) of Total Anginal Episodes, Prolonged Anginal Episodes (i.e., >20 Min) and Sublingual Nitrate Consumption During Four Weeks of Placebo and Mibefradil 100 mg Therapy in 20 Patients With the CSFP

Parameter	Placebo	Mibefradil 100 mg	p Value
Total angina (episodes/month)	34 (11, 56)	8 (3, 25)	<0.001
Prolonged angina (episodes/month)	8 (2, 24)	2 (0, 5)	<0.001
Sublingual nitrate use (tablets or sprays/month)	8 (1, 28)	3 (0, 6)	<0.01

CSFP = coronary slow flow phenomenon.

Table 4. The SF-36 Scores in 20 Patients With the Coronary Slow Flow Phenomenon, After Four Weeks of Placebo or Mibefradil Therapy

SF-36 Health Survey Concept	Placebo	Mibefradil	F*	p Value*
Physical health concepts				
Physical functioning	45 ± 5	53 ± 5	7.43	0.01
Bodily pain perception	37 ± 4	53 ± 6	6.76	0.02
General health perceptions	38 ± 3	45 ± 4	6.15	0.02
Role limitation due to physical health	9 ± 5	42 ± 10	10.03	0.005
Physical health summary score	31 ± 2	37 ± 2	11.97	0.003
Mental health concepts				
Vitality, energy, or fatigue	27 ± 3	40 ± 5	6.17	0.02
Social functioning	49 ± 5	58 ± 6	2.03	0.2
General mental health	58 ± 5	60 ± 5	0.32	0.5
Role limitation due to emotional problems	44 ± 10	61 ± 10	3.89	0.06
Mental health summary score	39 ± 3	42 ± 3	2.20	0.1

The Health Outcome Study Short Form (SF-36) scores are expressed as mean ± SEM. *F values and significance level in comparisons between placebo and mibefradil.

mibefradil can be safely and effectively used because it is well tolerated. Furthermore, patients with the CSFP are typically younger and do not have multiple medical problems so that mibefradil is frequently prescribed as monotherapy. Considering these practical aspects and the unique clinical properties of mibefradil, we believe mibefradil warrants orphan drug status for use in the CSFP.

In conclusion, the CSFP is an important, easily diagnosed, angiographic finding attributable to coronary microvascular dysfunction, which can be reversed by mibefradil. Patients with the CSFP often present initially with an acute coronary syndrome and account for 4% of unstable angina admissions (5). Their subsequent progress is frequently characterized by remitting, relapsing anginal episodes resulting in considerable impairment in quality of life, often in young patients. Currently available antianginal agents are usually of limited value, but we have demonstrated that mibefradil can both improve coronary flow and markedly ameliorate symptoms, thereby improving quality of life and recurrent hospitalizations in patients with the CSFP.

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